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TITLE: A Randomized, Controlled Trial of Meditation Compared to Exposure Therapy and Education Control on PTSD in Veterans

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14. ABSTRACT

This single-blinded, RCT will: 1) evaluate effects of Transcendental Meditation (TM) vs. Prolonged Exposure (PE) and PTSD health education control (EC), using the Clinician Administered PTSD Scale (CAPS) (primary outcome); 2) evaluate effects of TM vs. controls on PTSD symptoms (PCL-M), depressive symptoms and other psychological distress measures, quality of life, and physiological/biochemical stress markers; and 3) evaluate treatment compliance. The study will enroll 210 subjects (70 per group). The VA San Diego is the field site with testing conducted at 0 and 3 months The research will provide data on the feasibility and efficacy of TM as an alternative therapy for PTSD. Our collaborative group (Maharishi University of Management Research Institute, VA San Diego Healthcare System, University of California at San Diego) has made excellent progress. We are close to target for randomization, with 200 subjects randomized (target of 210) and have good treatment compliance, with over 70% treatment sessions attended. Post-testing compliance is greater than 80%. NCE was requested.

15. SUBJECT TERMS
PTSD, Meditation, Prolonged Exposure, Veterans

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TABLE OF CONTENTS

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a common and debilitating condition that affects up to 20% of all Veterans. PTSD is often a chronic problem for Veterans, affecting reintegration into society, family and marital relationships, sleep, employment stability, substance abuse rates, and risk for depression and suicide. Although standard treatments exist to treat PTSD, research shows that up to 50% of patients continue to have elevated symptoms. This suggests a need for developing and evaluating additional, alternative treatment options.

We are currently engaged in a collaborative research project that includes Maharishi University of Management Research Institute, VA San Diego Healthcare System, and the University of California at San Diego. This single-blinded, randomized controlled trial (RCT) will: 1) evaluate effects of Transcendental Meditation (TM) vs. Prolonged Exposure (PE) and a PTSD health education control (EC), using the Clinician Administered PTSD Scale (CAPS), as the primary outcome; 2) evaluate effects of TM vs. controls on PTSD symptoms (PCL-M), depressive symptoms and other psychological distress measures, quality of life, and physiological/ biochemical stress markers; and 3) evaluate treatment compliance. The study will enroll 210 subjects (70 per group) over four years. The intervention period for each arm is three months, with testing conducted at 0 and 3 months.

The research will provide important data on the feasibility and efficacy of the Transcendental Meditation program as an effective alternative therapy for PTSD. The results will serve to inform policy decisions on the study and application of this standardized and validated stress reduction program in Veteran populations.

BODY

The following tasks describe the actual Year 4 (Oct 1, 2015 thru Sept 30, 2016) achievements/milestones compared to the tasks originally outlined in the Statement of Work (SOW) (July, 2012, final-revised)

Task 1: Regulatory Review and Approval Processes (Completed)
Final DoD ORP approval was given for our staff to begin recruitment on May 31, 2013. This approval came after we made several human subjects-related adjustments based upon DoD ORP requests. The most significant of these requests involved receiving approval from the VASDHS IRB to do consenting over the phone prior to conducting initial phone screens. All subjects complete written informed consent, approved by the local IRB and DoD ORP, prior to baseline testing.

Task 2: Hiring and Training of Staff (Completed)
We completed the hiring and training of our three full-time staff coordinators during Year 1. After final approval from the DoD ORP, we were also able to officially hire the Prolonged Exposure study therapist – allowing us to have all of our study therapists in place.

Task 3: Development of Case Report Forms and Operation and Treatment Manuals (Completed)
We completed Case Report Forms and Operation and Treatment Manuals prior to beginning the study June 2013.

Task 4: Recruitment of Study Subjects (Consistent with Target Number)
After final DOD approval on May 31, 2013, we began recruitment of subjects. Since June 2013, we randomized (enrolled) 200 subjects, with a target goal of 210. To date, there have been approximately 538 phone screens with 441 potentially eligible, 288 consented (written consents) and completing baseline testing one, 200 completing baseline visit 2 and randomized. The number of subjects randomized over each quarter has been fairly consistent (see Supporting Data below).

Recruitment methods have included the use of posters, flyers, presentations to Veterans groups and community centers, placing information in VA and Veterans newsletters and presenting the study to VA healthcare providers for referrals. Weekly teleconference meetings are held on an ongoing basis with all staff and investigators, led by the initiating and partnering PIs.

Task 5: Testing of Subjects – baseline and 3-month post-testing (on target)
Baseline testing began June 2013. Through September 2016, 200 subjects, meeting eligibility criteria and completing baseline testing, were randomized (approximately 18% female; mean age= 48). Three-month posttesting compliance is approximately 83%.

Task 6: Delivery of Treatments (on target)
Through the end of September, 2016, 200 subjects have been randomized. Of these, over 90% of the randomized subjects have gotten into treatment or were scheduled for their first treatment session. Treatment sessions last approximately 75 minutes. Sessions are provided by trained instructors in each of the treatment arms: Transcendental Meditation, Prolonged Exposure, and PTSD Health Education, and are supervised by the research team for quality control.

No study-related adverse events have been reported to date.

Task 7: Treatment Compliance (on target)
Overall approximately 70% of the treatment sessions have been attended. Sessions are provided by trained instructors in each of the treatment arms: Transcendental Meditation, Prolonged Exposure, and PTSD Health Education, and are supervised by the research team for quality control. For home practice, over 70% of subjects have indicated compliance with their home practice program (at least once per day). These figures satisfy the 70% milestones for treatment compliance.

Task 8: Data Entry and Management (on target)
The Access database for data entry at VASDHS was developed and completed by study statistician, Maxwell Rainforth, and pilot tested by the VA data manager in Spring 2013. Data entered and stored is under strict quality control procedures. 100% of the

data received thus far has been entered. This meets our milestone established of collected data being entered.

Task 9: Data Analysis (on target)
Baseline data is shown in the Appendices section. The data is presented by treatment arm in a blinded manner. Data analysis procedures are on target.

Task 10: Overall Project Management (on target)
The initiating PI, Dr. Nidich at MUMRI, and partnering PI, Dr Rutledge at VASDHS, and their teams along with Dr. Mills at UC San Diego have been engaged in weekly or bi-monthly teleconference calls since the first month of the award, October 2012. In addition, Dr. Nidich and Dr. Rutledge frequently communicate each week on study management issues by phone and email. Other group members and staff have also frequently communicated by email and phone on a regular basis on study implementation issues, supervised by Drs. Nidich and Rutledge. Group conference calls with PIs, investigators, and staff will be ongoing throughout the trial.

Drs. Nidich, Rutledge, Mills, Rainforth attended all meetings of the Data Safety and Monitoring Board (DSMB), chaired by the study's medical monitor, Dr. Charles Elder, M.D. Other members of the DSMB include Dr. Kerri Boutelle, psychologist, Dr. Arpi Minassian, psychologist, and Dr. Loki Natarajan, biostatistician.

Task 11: Quarterly and Annual Reports
This document represents the study's fourth Annual report. All previous quarterly and annual reports to the DoD were written, submitted and received in a timely manner.

KEY ACCOMPLISHMENTS

- Study recruitment began in June 2013 immediately following DOD ORP human subjects approval.
- All study staff and treatment therapists were hired and trained as of the end of May 2013.
- We assembled a four-member Data Safety and Monitoring Board (DSMB) on July 18, 2013. The DSMB membership is chaired by Dr. Charles Elder, M.D., the study's medical monitor, and includes two clinical psychologists, who are active researchers and faculty at the UC San Diego Dept of Psychiatry and a biostatistician with the Dept. of Family and Preventive Medicine at UC San Diego. The DSMB met twice during the first year of the study and annually thereafter. The DSMB last met April, 2016 to review the progress of the study.
- As of Sept 30, 2016, 200 subjects have been recruited (210 target). Posttest compliance is >80% and intervention meeting attendance and home practice compliance is >70%.
- Dr. Nidich presented preliminary study results to the DoD In-Person Meeting at Ft. Detrick, MD September 8, 2016.

REPORTABLE OUTCOMES

There were no study publications or conference presentations during this past year. It is expected that there will be several publications and conferences presentations, based on the final study data in Winter and Spring, 2017.

Preliminary results of the study:
Transcendental Meditation(TM) showed significant decreases in severity of trauma symptoms compared to Health Education (HE) on both the CAPS and PCL-M. A significant decrease in co-morbid depression, using the PHQ-9, was also found in the TM group compared to HE. Between-group effect sizes for the TM group compared to HE ranged from .42 to .61. Within-group TM effect sizes ranged from .50 to .94. (See Supporting Data section.)

Prolonged Exposure (PE) showed significant decreases in severity of trauma symptoms compared to Health Education (HE) on both the CAPS and PCL-M. A significant decrease in depression was also found in the PE group compared to HE. Between-group effect sizes for the PE group compared to HE ranged from .32 to .36. Within-group PE effect sizes ranged from .40 to .69.

Non-inferiority analysis on study outcomes comparing Transcendental Meditation to Prolonged Exposure will be conducted with the final dataset (after completion of the study).

CONCLUSION

This report summarized the study progress through Year 4. We are meeting our Statement of Work targets for the study, and very close to achieving our recruitment goal. Study recruitment began on June 2013 immediately following DoD ORP human subjects approval. All study staff and treatment therapists have been hired and trained, operation manuals completed, and baseline testing and treatment sessions started. As of the end of September 2016, 200 subjects have been randomized, which is close to our target goal of 210 for the study. The April, 2016 Data Safety and Monitoring Board (DSMB) summary of meeting minutes is included in this annual report. There have been no “substantive” amendments to the study protocol. There were no study-related adverse events to date.

SUPPORTING DATA

Table 1: Overall Enrollment

Quarterly Period		# Randomized	Cumulative No.	Cum. Target
From	To			
6/1/13	9/30/13	24	24	23
10/1/13	12/31/13	17	41	41
1/1/14	3/31/14	19	60	58

4/1/13	**6/30/14**	**18**	**78**	**75**
7/1/14	**9/30/14**	**17**	**95**	**93**
10/1/14	**12/31/14**	**16**	**111**	**110**
1/1/15	**3/31/15**	**16**	**127**	**127**
4/1/15	**6/30/15**	**14**	**141**	**144**
7/1/15	**9/30/15**	**16**	**157**	**162**
10/1/15	**12/31/15**	**11**	**168**	**179**
1/1/16	**3/31/16**	**13**	**181**	**197**
4/1/16	**6/30/16**	**13**	**194**	**210**
7/1/16	**9/30/16**	**6**	**200**	**210**

Table 2: Sample Characteristics at Baseline: Demographics and Medical History by Intervention Group

Variable	**X**	**Y**	**Z**	**P value**
# Participants randomized	65	68	66	
Gender, % male	84.6%	82.4%	84.8%	0.910
Age, yrs				
Mean (std. dev.)	46.1 (16.5)	46.4 (14.3)	48.2 (15.2)	0.710
Median	45.0	47.5	49.0	
(Min, Max)	(23.0,82.0)	(24.0,76.0)	(24.0,85.0)	
Married / domestic partnership, %	53.8%	52.9%	51.5%	0.964
Education				0.173
Some high school				
High school graduate	9.2%	11.8%	20.0%	
Post secondary	90.8%	88.2%	80.0%	
Race				0.578
African American African descent	26.2%	29.4%	21.2%	
Asian American Asian descent	9.2%	7.4%	4.5%	

Caucasian	49.2%	55.9%	63.6%	
Native American	4.6%	0.0%	3.0%	
Other	10.8%	7.4%	7.6%	
Unknown				

Table 3: Comparison of Intervention Groups on Primary and Secondary Outcomes at Baseline

Variable	X	Y	Z	P value
CAPS total score	77.4 (18.7)	80.5 (17.7)	81.2 (17.2)	0.431
PCL-M score	58.5 (12.3)	60.5 (12.6)	61.1 (11.7)	0.446
PHQ-9 score	15.8 (5.5)	17.0 (6.1)	16.8 (5.0)	0.425
Profile of Mood States				
Tension/Anxiety	23.3 (6.9)	23.2 (8.3)	24.7 (7.3)	0.446
Depression/Deject	22.2 (11.1)	21.4 (12.8)	22.5 (11.0)	0.861
Anger/Hostility	19.5 (8.9)	19.0 (9.8)	20.9 (10.6)	0.496
Vigor/Activity	13.1 (5.8)	13.5 (6.9)	12.6 (6.6)	0.715
Fatigue/Inertia	14.2 (5.0)	13.8 (5.4)	15.6 (5.1)	0.101
Confusion/Bewilderment	18.8 (5.5)	18.1 (5.8)	18.6 (5.8)	0.759
POMS Total Score	84.9 (31.7)	82.0 (37.0)	89.9 (32.4)	0.404
Alcohol intake (drinks/week)	1.7 (3.2)	2.3 (5.9)	3.4 (6.3)	0.185
Cigarettes (no./day)	0.9 (3.6)	1.7 (3.9)	2.7 (5.9)	0.101
Satisfaction with Social Support	26.0 (8.7)	26.5 (9.3)	26.9 (8.6)	0.848
Quality of Life & Enjoyment Satisfaction Scale	44.4 (16.1)	42.9 (18.6)	41.8 (14.1)	0.663

All data are reported as means (SD). P-values for comparisons of groups are based on ANOVA.

Table 4: Comparison of Intervention Groups on PTSD Medication Status at Baseline

Variable	X	Y	Z	P value
AntiDepressants	23.1%	48.5%	34.8%	0.009

AntiConvulsants	9.2%	10.3%	9.1%	0.967
Anxiolytics	56.9%	66.2%	65.2%	0.485
Mood Stabilizers	15.4%	26.5%	18.2%	0.250
Antipsychotics	6.2%	19.1%	9.1%	0.049
Sleep Medications	46.2%	58.8%	48.5%	0.295
Any PTSD-MED	61.5%	80.9%	71.2%	0.048

P-values for comparisons of groups are based on chi-square tests.

Table 5: Change in Clinician-Administered Posttraumatic Stress Disorder (CAPS) Scores by Groups

	TM (n=50)	PE (n=50)	HE (n=53)
Mean change	-14.1 (-20.5, -7.6)	-11.4 (-18.5, -4.3)	-2.3 (-7.9, +3.3)
Effect size (between-group compared to health education); p value	d = .42; p = .009	d = .32; p = .044	
Clinically meaningful effect (% of participants)	62%	42%	30%

Notes: ANOVA completer analysis; mean (CI 95%), d = effect size; clinically meaningful effect = -10 points or greater.
Within-group effect sizes: TM: d= .50; PE: d = .40; HE: d = .08.

Table 6: Change in Posttraumatic Stress Disorder Checklist- Military (PCL-M) by Groups

	Transcendental Meditation	Prolonged Exposure	Health Education
Mean change	-12.9 (-16.2, -9.5)	-9.8 (-14.1, -5.4)	-3.9 (-7.5, -0.3)
Effect size (between-group compared to health education); p value	d = .55; p < .001	d = .36; p = .028	
Clinically meaningful effect (% of participants)	58%	42%	25%

Note: ANOVA; d = effect size; clinically meaningful effect = -10 points or greater.
Within-group effects sizes: TM: d= .79; PE: d = .60, HE: d = .24.

Table 7: Change in Patient Health Questionnaire (PHQ)- 9 Depression by Groups

	Transcendental Meditation	Prolonged Exposure	Health Education

Mean Change	-6.0 (-7.6, -4.5)	-4.4 (-6.0, -2.8)	-2.1 (-3.8, -0.4)
Effect size (between-group compared to health education); p value	d = .61; p < .001	d = .36; p = .046	
Clinically meaningful effect (% of participants)	70%	42%	35%

Note: ANOVA; d = effect size; clinically meaningful effect = -5 points or greater;
Within-group effects sizes: TM: d= .94; PE: d = .69; HE: d = .33

APPENDIX

1) Data & Safety Monitoring Board summary of meeting minutes, Thursday, April 21, 2016 11:00 am (PST)

Data & Safety Monitoring Board meeting minutes
Thursday, 4/21/2016 11:00 am (PST)

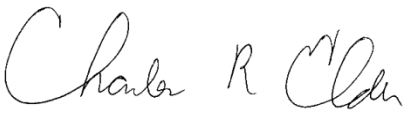
Attendees: Charles Elder, Kerri Boutelle, Arpi Minassian, Loki Natarajan, Thomas Rutledge, Sanford Nidich, Paul Mills, Mayra Gomez, Maxwell Rainforth, Alice Raven, Erica Matthews

- Overview of study – presentation provided by Dr. Sandy Nidich
- Review of study progress – Dr. Maxwell Rainforth presented data sets from June 2013 (start of study) – March 2016
    - Study sample characteristics
    - Recruitment, enrollment and retention
        - stratification is based on gender and time since trauma occurred (dichotomous variable, < 15 or > 15.1)
        - Overall 82.9 % retention rate at post-test. Excellent work!
            - DSMB suggested the potential of publishing a paper regarding strategies for upholding successful retention rates among a psychiatric population.

- Adherence, compliance
    - Attendance compliance at intervention varied across treatment groups. Y group exhibited a higher attendance rate of 75%
    - Compliance to home practice was highest among Y group with a 95.5% adherence. Groups X and Z demonstrated adherence to home practice within 80 % - 85% range
- Safety data and adverse events
    - No new study related adverse events to report.

- No executive session needed
- Debrief with review of recommendations
    - The P.I.'s notified the DSMB of their desire to request a no cost extension to the DOD and VMRF for the purpose of continuing recruitment and accruing additional participants. The DSMB endorsed this idea.
    - No further recommendations
- Conference call adjourned – DSMB will remain on standby in case a follow up meeting is required.

Respectfully submitted,



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DSMB Chair